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(54) Title: EPOTHILONE MINOR CONSTITUENTS			
(54) Bezeichnung: EPOTHILON-NEBENKOMPONENTEN			
(57) Abstract			
The invention relates to compounds which are obtained by fermenting DSM 6773, especially epothilones A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 and K and trans-epothilones C1 and C2.			
(57) Zusammenfassung			
Die Erfindung betrifft Verbindungen, die durch Fermentation von DSM 6773 erhältlich sind, insbesondere Epothilone A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 und K und Trans-Epothilone C1 und C2.			

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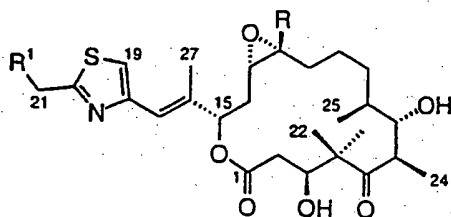
Epothilon-Nebenkomponenten

Die Erfindung betrifft Verbindungen, die im vorliegenden Zusammenhang als Epothilon-Nebenkomponenten bezeichnet werden, und zwar Verbindungen 5 bis 13 und 16 bis 39. Diese Verbindungen lassen sich durch Fermentation von DSM 6773 gemäß DE 41 38 042.8 gewinnen.

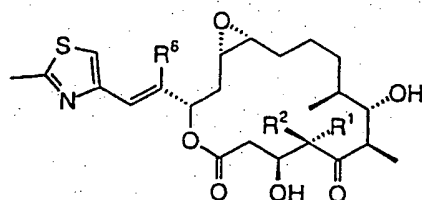
Kenndaten der erfindungsgemäßen Verbindungen sind im folgenden zusammengestellt.

Gewinnung: Die Aufarbeitung eines Rohepothilon-Gemischs, das durch Fermentation von DSM 6773 in einem 900 Liter-Fermentator gewonnen wurde, ist schematisch Fig. 1 bis 2 zu entnehmen.

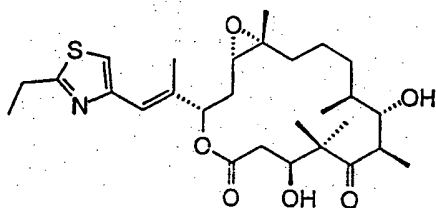
Aktivitäten: vgl. Tab. 1



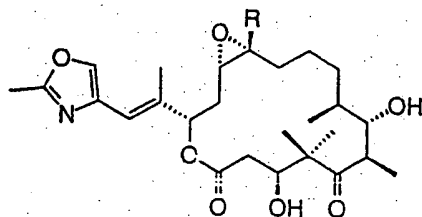
- Epothilone A (1) $R^1 = H; R = H$
 Epothilone B (2) $R^1 = H; R = Me$
 Epothilone E (3) $R^1 = OH; R = H$
 Epothilone F (4) $R^1 = OH; R = Me$



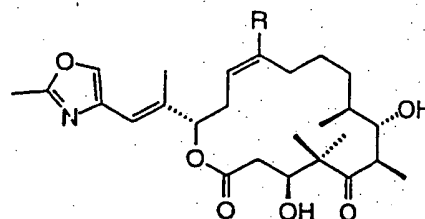
- Epothilone A₁ (5) $R^1 = H; R^2, R^8 = Me$
 Epothilone A₂ (6) $R^2 = H; R^1, R^8 = Me$
 Epothilone A₈ (7) $R^8 = H; R^1, R^2 = Me$
 Epothilone A₉ (8) $R^1 = CH_2OH; R^2, R^8 = Me$



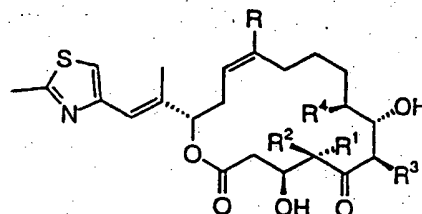
Epothilone B₁₀ (9)



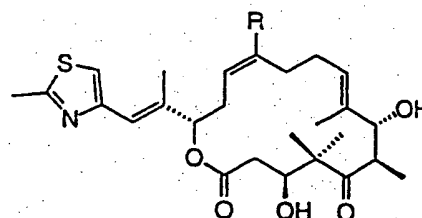
- Epothilone G₁ (10) $R = H$
 Epothilone G₂ (11) $R = Me$



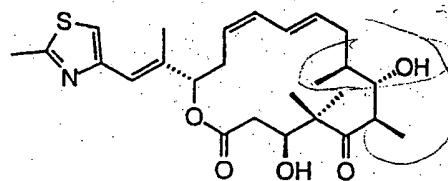
- Epothilone H₁ (12) $R = H$
 Epothilone H₂ (13) $R = Me$



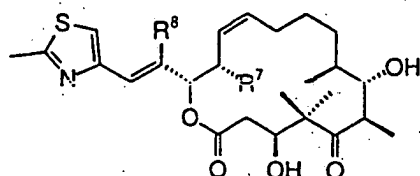
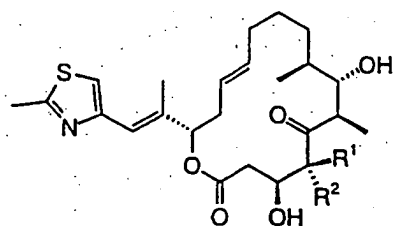
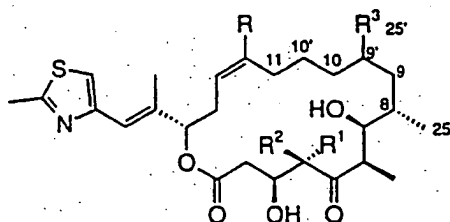
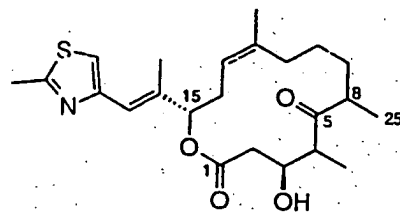
- Epothilone C (14) $R^1, R^2, R^3, R^4 = Me; R = H$
 Epothilone D (15) $R^1, R^2, R^3, R^4, R = Me$
 Epothilone C₁ (16) $R^1 = H; R^2, R^3, R^4 = Me; R = H$
 Epothilone D₁ (17) $R^1 = H; R^2, R^3, R^4 = Me; R = Me$
 Epothilone C₂ (18) $R^2 = H; R^1, R^3, R^4 = Me; R = H$
 Epothilone D₂ (19) $R^2 = H; R^1, R^3, R^4 = Me; R = Me$
 Epothilone C₃ (20) $R^3 = H; R^1, R^2, R^4 = Me; R = H$
 Epothilone C₄ (21) $R^4 = H; R^1, R^2, R^3 = Me; R = H$



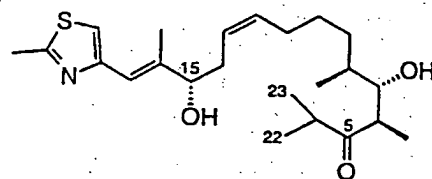
- Epothilone C₅ (22) $R = H$
 Epothilone D₅ (23) $R = Me$



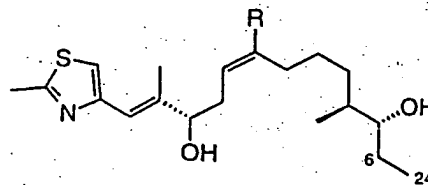
Epothilone C₆ (24)

Epothilone C₇ (25) R⁷ = OH; R⁸ = MeEpothilone C₈ (26) R⁸, R⁷ = HEpothilone C₉ (27) R⁸ = CH₂OH; R⁷ = Htrans-Epothilone C₁ (28) R¹ = H; R² = Metrans-Epothilone C₂ (29) R² = H; R¹ = MeEpothilone I₁ (30) R, R³ = H; R¹, R² = MeEpothilone I₂ (31) R = H; R¹, R², R³ = MeEpothilone I₃ (32) R¹, R², R³, R = MeEpothilone I₄ (33) R², R = H; R¹, R³ = MeEpothilone I₅ (34) R² = H; R¹, R³, R = MeEpothilone I₆ (35) R¹ = H; R², R³, R = Me

Epothilone K (36)



(37)



(38) R = H

(39) R = Me

Epothilone A₁ (5): colorless amorphous solid; $[\alpha]_D^{22}$ -69 (c 0.1, MeOH); UV (MeOH) λ_{\max} nm (ε) 208 (19600), 247 (13600); IR (KBr) ν_{\max} 3437, 2959, 2931, 2876, 1732, 1710, 1455, 1259, 978 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.95 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.68 (1H, dd, J = 4.4, 4.0 Hz, H-15), 4.12 (1H, m, H-3), 3.71 (1H, m, H-7), 3.52 (1H, bs, 7-OH), 3.37 (1H, bd, J = 7.5 Hz, 3-OH), 3.21 (1H, dq, J = 7.7, 7.0 Hz, H-4), 3.02 (1H, ddd, J = 9.2, 4.5, 2.8 Hz, H-13), 2.87 (1H, ddd, J = 8.3, 4.5, 3.7 Hz, H-12), 2.78 (1H, dd, J = 16.8, 4.3 Hz, H-2a), 2.70 (3H, s, H-21), 2.66 (1H, dq, J = 3.9, 7.0 Hz, H-6), 2.65 (1H, dd, J = 16.8, 5.2 Hz, H-2b), 2.16 (1H, ddd, J = 15.4, 4.4, 2.8 Hz, H-14a), 2.12 (3H, bs, H-27), 1.91 (1H, ddd, J = 15.4, 9.2, 4.0 Hz, H-14b), 1.63 (1H, m, H-10a), 1.62 (2H, m, H-11), 1.59 (1H, m, H-9a), 1.52 (1H, m, H-10b), 1.39 (1H, m, H-8), 1.35 (1H, m, H-9b), 1.211 (3H, d, J = 7.0 Hz, H-23), 1.207 (3H, d, J = 7.0 Hz, H-24), 0.89 (3H, d, J = 6.9 Hz, H-25); EIMS m/z 479 $[\text{M}]^+$ (21), 322 (31), 306 (65), 304 (47), 168 (45), 166 (73), 164 (100), 151 (30), 140 (35); HREIMS m/z 479.2317 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_5\text{S}$, 479.2342).

Epothilone A₂ (6): colorless amorphous solid; $[\alpha]_D^{22}$ +12.0 (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ε) 210 (15100), 248 (15500); IR (KBr) ν_{\max} 3438, 2963, 2929, 2875, 1734, 1706, 1458, 1262, 981 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.98 (1H, s, H-19), 6.63 (1H, bs, H-17), 5.40 (1H, dd, J = 8.3, 3.4 Hz, H-15), 4.26 (1H, ddd, J = 8.5, 4.8, 4.7 Hz, H-3), 3.85 (1H, dd, J = 7.9,

2.6 Hz, H-7), 3.54 (1H, bs, 3-OH), 3.09 (1H, dq, $J = 4.8, 7.0$ Hz, H-4), 3.01 (1H, ddd, $J = 8.3, 4.8, 4.6$ Hz, H-13), 2.98 (1H, dq, $J = 7.9, 7.0$ Hz, H-6), 2.89 (1H, ddd, $J = 6.7, 4.6, 4.4$ Hz, H-12), 2.68 (3H, s, H-21), 2.60 (1H, dd, $J = 15.1, 8.5$ Hz, H-2a), 2.52 (1H, bs, 7-OH), 2.50 (1H, dd, $J = 15.1, 4.7$ Hz, H-2b), 2.18 (1H, ddd, $J = 15.0, 4.8, 3.4$ Hz, H-14a), 2.11 (3H, d, $J = 1.3$ Hz, H-27), 1.82 (1H, ddd, $J = 15.0, 8.3, 8.1$ Hz, H-14b), 1.63 (1H, m, H-8), 1.61 (2H, m, H-11a and H-10a), 1.46 (1H, m, H-11b), 1.39 (2H, m, H-9), 1.31 (1H, m, H-10b), 1.22 (3H, d, $J = 7.0$ Hz, H-24), 1.15 (3H, d, $J = 7.0$ Hz, H-22), 1.01 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 216.2 (s, C-5), 170.1 (s, C-1), 164.9 (s, C-20), 152.0 (s, C-18), 137.0 (s, C-16), 120.3 (d, C-17), 116.5 (d, C-19), 76.7 (d, C-15), 75.6 (d, C-7), 69.1 (d, C-3), 57.1 (d, C-12), 54.3 (d, C-13), 50.3 (d, C-4), 49.6 (d, C-6), 39.4 (t, C-2), 35.5 (d, C-8), 32.2 (t, C-14), 29.6 (t, C-9), 27.6 (t, C-11), 23.9 (t, C-10), 19.2 (q, C-21), 18.0 (q, C-25), 15.6 (q, C-27), 13.9 (q, C-24), 12.4 (q, C-22); EIMS m/z 479 $[\text{M}]^+$ (18), 322 (38), 306 (78), 304 (59), 168 (48), 166 (96), 164 (100), 151 (33), 140 (38); HREIMS m/z 479.2318 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_5\text{S}$, 479.2342).

Epothilone A₃ (7): colorless amorphous solid; $[\alpha]_D^{22} -76.2$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 210 (15300), 248 (15500); IR (KBr) ν_{max} 3440, 2967, 2932, 2876, 1736, 1691, 1467, 1252, 979 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.95 (1H, s, H-19), 6.64 (1H, dd, $J = 15.6, 0.9$ Hz, H-17), 6.52 (1H, dd, $J = 15.6, 6.6$ Hz, H-16), 5.68 (1H, dddd, $J = 7.8, 6.6, 3.2, 0.9$ Hz, H-15), 4.11 (1H, ddd, $J = 10.1, 6.6, 3.5$ Hz, H-3), 3.78 (1H, ddd, $J = 5.2, 3.2, 3.2$ Hz, H-7), 3.66 (1H, d, $J = 6.6$ Hz, 3-OH), 3.23 (1H, dq, $J = 5.2, 6.9$ Hz, H-6), 3.08 (1H, ddd, $J = 7.3, 5.5, 4.1$ Hz, H-13), 2.90 (1H, ddd, $J = 6.6, 4.6, 4.1$ Hz, H-12), 2.69 (3H, s, H-21), 2.52 (1H, dd, $J = 14.7, 10.1$ Hz, H-2a), 2.44 (1H, bd, $J = 3.2$ Hz, 7-OH), 2.41 (1H, dd, $J = 14.7, 3.5$ Hz, H-2b), 2.10

(1H, ddd, $J = 15.0, 5.5, 3.2$ Hz, H-14a), 1.90 (1H, ddd, $J = 15.0, 7.8, 7.3$ Hz, H-14b), 1.71 (1H, m, H-8), 1.65 (1H, m, H-11a), 1.50 (1H, m, H-10a), 1.47 (1H, m, H-11b), 1.40 (2H, m, H-9), 1.39 (1H, m, H-10b), 1.33 (3H, s, H-23), 1.16 (3H, d, $J = 6.9$ Hz, H-24), 1.08 (3H, s, H-22), 0.98 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR (CDCl_3 , 75 MHz) δ 220.3 (s, C-5), 170.7 (s, C-1), 166.5 (s, C-20), 152.2 (s, C-18), 128.4 (d, C-16), 125.9 (d, C-17), 116.4 (d, C-19), 75.0 (d, C-7), 73.6 (d, C-3), 72.7 (d, C-15), 57.3 (d, C-12), 54.1 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.9 (t, C-2), 36.3 (d, C-8), 32.5 (t, C-14), 30.3 (t, C-9), 26.7 (t, C-11), 24.0 (t, C-10), 21.3 (q, C-23), 21.0 (q, C-22), 19.3 (q, C-21), 17.1 (q, C-25), 14.5 (q, C-24); EIMS m/z 479 $[\text{M}]^+$ XXX; HRDCIMS m/z 480.2401 (calcd. for $\text{C}_{25}\text{H}_{38}\text{NO}_6\text{S}$, 480.2401).

Epothilone A₉ (8): colorless amorphous solid; $[\alpha]_D^{25} -37.6$ (c 0.5, MeOH); UV (MeOH) λ_{max} nm (ϵ) 211 (15500), 253 (14100); IR (KBr) ν_{max} 3423, 2965, 2932, 2877, 1736, 1690, 1463, 1249, 1014, 979 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.10 (1H, s, H-19), 6.72 (1H, dd, $J = 10.7, 4.3$ Hz, 27-OH), 6.60 (1H, bs, H-17), 5.69 (1H, dd, $J = 11.6, 2.0$ Hz, H-15), 5.59 (1H, d, $J = 6.6$ Hz, 3-OH), 4.49 (1H, ddd, $J = 12.9, 4.3, 1.2$ Hz, H-27a), 4.27 (1H, ddd, $J = 11.6, 6.6, 2.9$ Hz, H-3), 4.11 (1H, ddd, $J = 12.9, 10.7, 1.0$ Hz, H-27b), 3.71 (1H, ddd, $J = 4.8, 3.0, 2.8$ Hz, H-7), 3.17 (1H, dq, $J = 3.0, 6.8$ Hz, H-6), 3.04 (1H, ddd, $J = 9.7, 3.6, 2.2$ Hz, H-13), 2.93 (1H, bs, 7-OH), 2.91 (1H, ddd, $J = 9.7, 3.6, 2.7$ Hz, H-12), 2.72 (3H, s, H-21), 2.48 (1H, dd, $J = 14.2, 11.6$ Hz, H-2a), 2.11 (1H, dd, $J = 14.2, 2.9$ Hz, H-2b), 2.03 (1H, ddd, $J = 14.7, 2.2, 2.0$ Hz, H-14a), 1.86 (1H, m, H-11a), 1.85 (1H, m, H-14b), 1.79 (1H, m, H-8), 1.52 (1H, m, H-10a), 1.37 (3H, m, H-9 and H-10b), 1.37 (3H, s, H-23), 1.36 (1H, m, H-11b), 1.19 (3H, d, $J = 6.8$ Hz, H-24), 1.02 (3H, d, $J = 7.1$ Hz, H-25), 1.00 (3H, s, H-22); ^{13}C NMR (CDCl_3 , 75 MHz) δ 220.5 (s, C-5).

170.2 (s, C-1), 167.5 (s, C-20), 150.7 (s, C-18), 138.9 (s, C-16), 125.2 (d, C-17), 119.5 (d, C-19), 76.7 (d, C-15), 73.4 (d, C-7), 70.4 (d, C-3), 57.7 (d, C-12), 57.2 (t, C-27), 55.3 (d, C-13), 54.2 (s, C-4), 41.3 (d, C-6), 40.7 (t, C-2), 37.5 (d, C-8), 31.8 (t, C-14), 31.2 (t, C-9), 28.0 (t, C-11), 23.7 (q, C-23), 23.2 (t, C-10), 19.2 (q, C-21), 16.8 (q, C-22), 15.8 (q, C-25), 13.5 (q, C-24); EIMS m/z 509 [M]⁺ (9), 491 (4), 322 (28), 321 (25), 180 (45), 167 (40), 166 (100), 165 (49), 154 (47), 138 (33); HREIMS m/z 509.2467 (calcd. for C₂₆H₃₉NO₇S, 509.2447).

Epothilone B₁₀ (9): colorless amorphous solid; $[\alpha]_D^{22}$ -27 (c 0.15, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 212 (15800), 247 (12500); IR (KBr) ν_{\max} 3434, 2962, 2930, 2876, 2858, 1733, 1692, 1461, 1259, 1052, 981 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 6.99 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.42 (1H, dd, J = 8.0, 3.0 Hz, H-15), 4.25 (1H, ddd, J = 9.5, 6.3, 2.8 Hz, H-3), 4.23 (1H, bs, 3-OH), 3.77 (1H, ddd, J = 4.0, 3.9, 3.8 Hz, H-7), 3.30 (1H, dq, J = 4.0, 6.9 Hz, H-6), 3.01 (2H, q, J = 7.6 Hz, H-21), 2.81 (1H, dd, J = 7.7, 4.6 Hz, H-13), 2.68 (1H, bs, 7-OH), 2.54 (1H, dd, J = 13.9, 9.5 Hz, H-2a), 2.36 (1H, dd, J = 13.9, 2.8 Hz, H-2b), 2.11 (1H, ddd, J = 15.3, 4.6, 3.0 Hz, H-14a), 2.09 (3H, s, H-27), 1.91 (1H, ddd, J = 15.3, 8.0, 7.7 Hz, H-14b), 1.74 (1H, m, H-8), 1.73 (1H, m, H-11a), 1.51 (1H, m, H-10a), 1.41 (1H, m, H-11b), 1.39 (3H, t, J = 7.6 Hz, H-28), 1.38 (3H, m, H-9 and H-10b), 1.37 (3H, s, H-23), 1.28 (3H, s, H-26), 1.17 (3H, d, J = 6.9 Hz, H-24), 1.09 (3H, s, H-22), 1.01 (3H, d, J = 7.0 Hz, H-25); EIMS m/z 521 [M]⁺ (22), 449 (7), 350 (18), 334 (57), 248 (16), 234 (27), 196 (41), 182 (59), 180 (96), 178 (100), 166 (44), 154 (44); HREIMS m/z 521.2808 (calcd. for C₂₈H₄₃NO₆S, 521.2811).

Epothilone G, (10): colorless amorphous solid; $[\alpha]_D^{22}$ -39.7 (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 203 (15200), 236 (15100); IR (KBr) ν_{\max} 3456, 2962, 2933, 2876, 1736,

1691, 1585, 1466, 1262, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.47 (1H, s, H-19), 6.33 (1H, bs, H-17), 5.42 (1H, dd, $J = 8.3, 2.9$ Hz, H-15), 4.11 (1H, ddd, $J = 10.1, 6.1, 3.4$ Hz, H-3), 3.78 (1H, bddd, $J = 5.2, 3.5, 3.5$ Hz, H-7), 3.63 (1H, bd, $J = 6.1$ Hz, 3-OH), 3.21 (1H, dq, $J = 5.2, 7.0$ Hz, H-6), 3.00 (1H, ddd, $J = 7.7, 4.8, 4.2$ Hz, H-13), 2.88 (1H, ddd, $J = 7.1, 4.2, 4.2$ Hz, H-12), 2.53 (1H, dd, $J = 14.8, 10.1$ Hz, H-2a), 2.51 (1H, bd, $J = 3.5$ Hz, 7-OH), 2.43 (1H, dd, $J = 14.8, 3.4$ Hz, H-2b), 2.43 (3H, s, H-21), 2.07 (1H, ddd, $J = 15.1, 4.8, 2.9$ Hz, H-14a), 1.99 (3H, d, $J = 1.3$ Hz, H-27), 1.86 (1H, ddd, $J = 15.1, 8.3, 7.7$ Hz, H-14b), 1.71 (1H, m, H-8), 1.69 (1H, m, H-11a), 1.53 (1H, m, H-10a), 1.42 (1H, m, H-11b), 1.40 (3H, m, H-9 and H-10b), 1.34 (3H, s, H-23), 1.16 (3H, d, $J = 7.0$ Hz, H-24), 1.09 (3H, s, H-22), 0.99 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.1 (s, C-5), 170.5 (s, C-1), 161.0 (s, C-20), 137.4 (s, C-18), 136.7 (s, C-16), 135.9 (d, C-19), 116.4 (d, C-17), 76.4 (d, C-15), 74.9 (d, C-7), 73.7 (d, C-3), 57.4 (d, C-12), 54.4 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.8 (t, C-2), 36.2 (d, C-8), 31.4 (t, C-14), 30.4 (t, C-9), 27.0 (t, C-11), 23.9 (t, C-10), 21.3 (q, C-23), 21.2 (q, C-22), 17.2 (q, C-25), 15.8 (q, C-27), 14.4 (q, C-24), 13.8 (q, C-21); EIMS m/z 477 $[\text{M}]^+$ (4), 405 (7), 290 (40), 152 (39), 150 (100), 148 (23), 124 (23); HREIMS m/z 477.2684 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_7$, 477.2727).

Epothilone G₂ (11): colorless amorphous solid; $[\alpha]_D^{22} -22.6$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 202 (21500), 236 (14800); IR (KBr) ν_{max} 3456, 2965, 2934, 2877, 1737, 1690, 1586, 1464, 1250, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (1H, s, H-19), 6.33 (1H, bs, H-17), 5.43 (1H, dd, $J = 7.1, 3.6$ Hz, H-15), 4.12 (1H, ddd, $J = 9.9, 6.4, 3.4$ Hz, H-3), 3.77 (1H, ddd, $J = 4.7, 4.4, 4.1$ Hz, H-7), 3.83 (1H, bd, $J = 6.4$ Hz, 3-OH), 3.30 (1H, dq, $J = 4.7, 6.9$

Hz, H-6), 2.78 (1H, dd, $J = 7.0, 5.4$ Hz, H-13), 2.54 (1H, dd, $J = 14.3, 9.9$ Hz, H-2a), 2.51 (1H, bd, $J = 4.1$ Hz, 7-OH), 2.44 (3H, s, H-21), 2.40 (1H, dd, $J = 14.3, 3.4$ Hz, H-2b), 2.03 (1H, ddd, $J = 15.2, 5.4, 3.6$ Hz, H-14a), 2.00 (3H, d, $J = 1.3$ Hz, H-27), 1.92 (1H, ddd, $J = 15.1, 7.1, 7.0$ Hz, H-14b), 1.71 (1H, m, H-8), 1.68 (1H, m, H-11a), 1.51 (1H, m, H-10a), 1.42 (1H, m, H-11b), 1.39 (3H, m, H-9 and H-10b), 1.35 (3H, s, H-23), 1.26 (3H, s, H-26), 1.16 (3H, d, $J = 6.9$ Hz, H-24), 1.07 (3H, s, H-22), 0.99 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.7 (s, C-5), 170.5 (s, C-1), 161.0 (s, C-20), 137.4 (s, C-18), 136.5 (s, C-16), 135.9 (d, C-19), 116.3 (d, C-17), 76.6 (d, C-15), 74.6 (d, C-7), 73.5 (d, C-3), 61.3 (s, C-12), 61.1 (d, C-13), 52.7 (s, C-4), 43.4 (d, C-6), 39.0 (t, C-2), 36.5 (d, C-8), 32.0 (t, C-11), 31.8 (t, C-14), 30.8 (t, C-9), 22.8 (t, C-10), 22.9 (q, C-26), 21.0 (q, C-23), 20.8 (q, C-22), 17.2 (q, C-25), 15.9 (q, C-27), 14.1 (q, C-24), 13.8 (q, C-21); EIMS m/z 491 $[\text{M}]^+$ (21), 419 (6), 320 (18), 304 (39), 166 (42), 152 (57), 150 (100), 149 (44), 148 (58), 124 (35), 109 (33); HREIMS m/z 491.2878 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_7$, 491.2883).

Epothilone H_1 (12): colorless amorphous solid; $[\alpha]_D^{22} -84.2$ (c 0.2, MeOH); UV (MeOH) λ_{max} nm (ϵ) 203 (19600), 237 (12000); IR (KBr) ν_{max} 3436, 2933, 2880, 2860, 1734, 1688, 1585, 1251, 1007 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.47 (1H, s, H-19), 6.31 (1H, bs, H-17), 5.43 (1H, ddd, $J = 10.6, 10.2, 4.5$ Hz, H-12), 5.36 (1H, dddd, $J = 10.6, 9.6, 5.0, 1.3$ Hz, H-13), 5.30 (1H, dd, $J = 9.9, 2.0$ Hz, H-15), 4.16 (1H, ddd, $J = 11.2, 5.3, 2.8$ Hz, H-3), 3.73 (1H, ddd, $J = 3.9, 2.5, 2.3$ Hz, H-7), 3.12 (1H, dq, $J = 2.3, 6.9$ Hz, H-6), 2.92 (1H, d, $J = 2.5$ Hz, 7-OH), 2.91 (1H, d, $J = 5.3$ Hz, 7-OH), 2.66 (1H, ddd, $J = 15.1, 9.9, 9.6$ Hz, H-14a), 2.50 (1H, dd, $J = 15.4, 11.2$ Hz, H-2a), 2.43 (3H, s, H-21), 2.37 (1H, dd, $J = 15.4, 2.8$ Hz, H-2b), 2.23

(1H, m, H-14b), 2.18 (1H, m, H-11a), 2.01 (1H, m, H-11b), 2.08 (3H, d, $J = 1.3$ Hz, H-27), 1.74 (1H, m, H-8), 1.65 (1H, m, H-10a), 1.33 (1H, m, H-9a), 1.31 (3H, s, H-23), 1.19 (1H, m, H-10b), 1.18 (1H, m, H-9b), 1.17 (3H, d, $J = 6.9$ Hz, H-24), 1.08 (3H, s, H-22), 0.99 (3H, d, $J = 7.1$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 461 $[\text{M}]^+$ (6), 310 (5), 274 (10), 273 (7), 171 (63), 152 (100), 148 (18), 111 (15); HREIMS m/z 461.2743 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_6$, 461.2777).

Epothilone H_2 (13): colorless amorphous solid; $[\alpha]_D^{22} -44.4$ (c 0.25, MeOH); UV (MeOH) λ_{max} nm (ϵ) 203 (14500), 236 (12200); IR (KBr) ν_{max} 3436, 2967, 2935, 2880, 1734, 1690, 1586, 1251, 1007 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.46 (1H, s, H-19), 6.30 (1H, bs, H-17), 5.23 (1H, dd, $J = 9.8, 2.1$ Hz, H-15), 5.12 (1H, dd, $J = 10.1, 5.3$ Hz, H-13), 4.20 (1H, ddd, $J = 10.8, 5.7, 2.9$ Hz, H-3), 3.71 (1H, ddd, $J = 3.8, 2.6, 2.6$ Hz, H-7), 3.14 (1H, dq, $J = 2.6, 6.9$ Hz, H-6), 2.93 (d, $J = 5.7$ Hz, 3-OH), 2.90 (1H, bd, $J = 2.6$ Hz, 7-OH), 2.62 (1H, ddd, $J = 15.1, 9.8, 9.8$ Hz, H-14a), 2.46 (1H, dd, $J = 15.1, 10.8$ Hz, H-2a), 2.43 (3H, s, H-21), 2.32 (1H, dd, $J = 15.1, 2.9$ Hz, H-2b), 2.29 (1H, m, H-11a), 2.19 (1H, bd, $J = 15.1$ Hz, H-14b), 1.97 (3H, d, $J = 1.3$ Hz, H-27), 1.87 (1H, m, H-11b), 1.73 (1H, m, H-8), 1.67 (1H, m, H-10a), 1.65 (3H, bs, H-26), 1.32 (3H, s, H-23), 1.26 (2H, m, H-9), 1.24 (1H, m, H-10b), 1.18 (3H, d, $J = 6.9$ Hz, H-24), 1.07 (3H, s, H-22), 1.00 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.6 (s, C-5), 170.3 (s, C-1), 161.0 (s, C-20), 138.6 (s, C-12), 138.4 (s, C-16), 137.5 (s, C-18), 135.6 (d, C-19), 120.8 (d, C-13), 115.8 (d, C-17), 78.9 (d, C-15), 74.3 (d, C-7), 72.7 (d, C-3), 53.3 (s, C-4), 42.0 (d, C-6), 39.6 (t, C-2), 38.6 (d, C-8), 32.4 (t, C-14), 31.9 (t, C-9), 31.6 (t, C-11), 25.6 (t, C-10), 23.0 (q, C-26), 22.8 (q, C-23), 18.8 (q, C-22), 16.1 (q, C-27), 15.9 (q, C-25), 13.8 (q, C-21), 13.6 (q, C-24); EIMS m/z 475 $[\text{M}]^+$ (11), 288 (9), 287 (5), 188 (7), 171 (32), 152 (100),

111 (10); HREIMS m/z 475.2913 (calcd. for $C_{27}H_{41}NO_6$, 475.2934).

Epothilone C₁ (16): colorless amorphous solid; $[\alpha]_D^{22}$ -114.0 (c 10.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 211 (16500), 248 (12500); IR (KBr) ν_{\max} 3440, 2933, 2877, 2858, 1730, 1708, 1457, 1244, 981 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.96 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.47 (1H, dd, J = 9.2, 3.0 Hz, H-15), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 4.40 (1H, ddd, J = 6.2, 6.1, 6.1 Hz, H-3), 3.69 (1H, dd, J = 5.7, 3.6 Hz, H-7), 3.01 (1H, dq, J = 5.7, 6.9 Hz, H-6), 3.01 (1H, bs, 3-OH), 2.84 (1H, dq, J = 5.2, 7.0 Hz, H-4), 2.68 (3H, s, H-21), 2.66 (1H, ddd, J = 16.4, 9.2, 7.3 Hz, H-14a), 2.64 (1H, dd, J = 15.9, 7.1 Hz, H-2a), 2.54 (1H, dd, J = 15.9, 6.1 Hz, H-2b), 2.38 (1H, bd, J = 16.4 Hz, H-14b), 2.35 (1H, bs, 7-OH), 2.07 (3H, bs, H-27), 2.03 (2H, m, H-11), 1.62 (1H, m, H-10a), 1.53 (1H, m, H-8), 1.35 (1H, m, H-9a), 1.22 (1H, m, H-9b), 1.19 (3H, d, J = 6.9 Hz, H-24), 1.14 (3H, d, J = 6.9 Hz, H-23), 1.10 (1H, m, H-10b), 0.95 (3H, d, J = 6.9 Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (5), 324 (8), 290 (8), 204 (7), 168 (100), 164 (15), 139 (36); HREIMS m/z 463.2381 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

Epothilone D₁ (17): colorless amorphous solid; $[\alpha]_D^{22}$ -118.6 (c 0.5, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 208 (18300), 249 (11900); IR (KBr) ν_{\max} 3439, 2965, 2934, 2877, 1729, 1707, 1456, 1250, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.98 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.51 (1H, dd, $J = 9.5, 3.4$ Hz, H-15), 5.16 (1H, dd, $J = 8.0, 4.2$ Hz, H-13), 4.42 (1H, ddd, $J = 7.1, 6.3, 5.5$ Hz, H-3), 3.70 (1H, dd, $J = 6.5, 2.9$ Hz, H-7), 3.07 (1H, dq, $J = 6.5, 6.9$ Hz, H-6), 2.95 (1H, dq, $J = 4.7, 7.0$ Hz, H-4), 2.71 (3H, s, H-21), 2.69 (1H, dd, $J = 16.0, 6.3$ Hz, H-2a), 2.64 (1H, m, H-14a), 2.59 (1H, dd, $J = 16.0, 7.1$ Hz, H-2b), 2.46 (1H, bs, 3-OH), 2.38 (1H, bd, $J = 16.0$ Hz, H-14b), 2.19 (1H, ddd, $J = 13.3, 8.6, 5.7$ Hz, H-11a), 2.10 (3H, d, $J = 1.4$ Hz, H-27), 2.02 (1H, bs, 7-OH), 1.91 (1H, ddd, $J = 13.3, 6.0, 6.0$ Hz, H-11b), 1.68 (1H, m, H-10a), 1.66 (3H, bs, H-26), 1.53 (1H, m, H-8), 1.37 (1H, m, H-9a), 1.26 (1H, m, H-9b), 1.24 (3H, d, $J = 6.9$ Hz, H-24), 1.19 (1H, m, H-10b), 1.14 (3H, d, $J = 7.0$, H-23), 0.99 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 217.0 (s, C-5), 169.7 (s, C-1), 165.0 (s, C-20), 152.2 (s, C-18), 138.5 (s, C-12), 137.7 (s, C-16), 120.7 (d, C-13), 120.1 (d, C-17), 116.3 (d, C-19), 78.8 (d, C-15), 77.2 (d, C-7), 67.7 (d, C-3), 52.1 (d, C-4), 46.5 (d, C-6), 40.6 (t, C-2), 37.6 (d, C-8), 32.3 (t, C-14), 31.8 (t, C-11), 29.5 (t, C-9), 25.5 (t, C-10), 23.1 (q, C-26), 19.2 (q, C-21), 15.5 (q, C-27), 16.6 (q, C-25), 14.5 (q, C-24), 9.7 (q, C-23); EIMS m/z 477 $[\text{M}]^+$ (13), 304 (19), 303 (31), 218 (40), 204 (41), 163 (100), 164 (45), 157 (25), 139 (18); HREIMS m/z 477.2544 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$, 477.2549).

Epothilone C₂ (18): colorless amorphous solid; $[\alpha]_D^{22}$ -11.6 (c 10.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 212 (15500), 249 (12100); IR (KBr) ν_{\max} 3428, 2962, 2929, 2877, 2859, 1734, 1705, 1460, 1251, 982 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.99 (1H, s, H-19), 6.66 (1H,

bs, H-17), 5.55 (1H, ddd, $J = 10.4, 9.2, 6.1$ Hz, H-12), 5.38 (1H, ddd, $J = 10.4, 9.3, 6.2$ Hz, H-13), 5.22 (1H, dd, $J = 8.8, 2.8$ Hz, H-15), 4.42 (1H, dddd, $J = 9.4, 5.6, 4.2, 4.1$ Hz, H-3), 3.93 (1H, d, $J = 5.6$ Hz, 3-OH), 3.86 (1H, m, H-7), 3.15 (1H, bs, 7-OH), 3.12 (1H, dq, $J = 4.2, 7.0$ Hz, H-4), 3.00 (1H, dq, $J = 6.9, 7.0$ Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dddd, $J = 15.1, 9.3, 8.8, 0.8$ Hz, H-14a), 2.58 (1H, dd, $J = 15.4, 9.4$ Hz, H-2a), 2.38 (1H, dd, $J = 15.4, 4.1$ Hz, H-2b), 2.31 (1H, ddd, $J = 15.1, 6.2, 2.8$ Hz, H-14b), 2.08 (3H, d, $J = 1.3$ Hz, H-27), 2.15 (1H, m, H-11a), 2.04 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.59 (1H, m, H-10a), 1.43 (1H, m, H-9a), 1.31 (1H, m, H-9b), 1.26 (3H, d, $J = 7.0$ Hz, H-24), 1.15 (3H, d, $J = 7.0$ Hz, H-23), 1.11 (1H, m, H-10b), 1.00 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (7), 324 (7), 306 (8), 290 (17), 168 (100), 164 (14), 139 (27); HREIMS m/z 463.2392 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

Epithilone D: (19): colorless amorphous solid; $[\alpha]_D^{22} -12.5$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 210 (15400), 248 (11200); IR (KBr) ν_{max} 3436, 2965, 2930, 2877, 1732, 1705, 1458, 1253, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.97 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.18 (1H, dd, $J = 7.9, 4.9$ Hz, H-15), 5.18 (1H, ddd, $J = 9.6, 5.4, 1.0$ Hz, H-13), 4.27 (1H, m, H-3), 3.88 (1H, dd, $J = 5.6, 4.6$ Hz, H-7), 3.19 (1H, bs, 3-OH), 3.07 (1H, dq, $J = 4.3, 7.0$ Hz, H-4), 2.95 (1H, dq, $J = 5.6, 7.0$ Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, $J = 14.9, 7.8$ Hz, H-2a), 2.56 (1H, ddd, $J = 14.7, 9.6, 7.9$ Hz, H-14a), 2.43 (1H, dd, $J = 14.9, 5.6$ Hz, H-2b), 2.38 (1H, bs, 7-OH), 2.26 (1H, ddd, $J = 14.5, 5.4, 4.9$ Hz, H-14b), 2.19 (1H, ddd, $J = 13.0, 10.4, 5.4$ Hz, H-11a), 2.10 (3H, d, $J = 1.4$ Hz, H-27), 1.95 (1H, ddd, $J = 13.0, 10.3, 5.3$ Hz, H-11b), 1.72 (1H, m, H-8), 1.68 (3H, bs, H-26), 1.61 (1H, m, H-10a), 1.39 (2H, m, H-9), 1.21 (1H, m, H-10b).

1.19 (3H, d, $J = 6.9$ Hz, H-24), 1.17 (3H, d, $J = 7.0$, H-22), 1.00 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 216.8 (s, C-5), 170.4 (s, C-1), 164.9 (s, C-20), 152.3 (s, C-18), 139.8 (s, C-12), 137.5 (s, C-16), 120.5 (d, C-17), 119.2 (d, C-13), 116.3 (d, C-19), 80.0 (d, C-15), 74.3 (d, C-7), 69.7 (d, C-3), 48.6 (d, C-4), 48.4 (d, C-6), 39.9 (t, C-2), 36.6 (d, C-8), 32.2 (t, C-14), 32.7 (t, C-11), 30.9 (t, C-9), 26.0 (t, C-10), 23.6 (q, C-26), 19.2 (q, C-21), 15.4 (q, C-27), 17.1 (q, C-25), 12.4 (q, C-24), 12.7 (q, C-23); EIMS m/z 477 $[\text{M}]^+$ (22), 304 (19), 303 (17), 218 (22), 204 (25), 168 (100), 164 (28), 157 (31), 139 (21); HREIMS m/z 477.2545 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$, 477.2549).

Epithilone C₃ (20): colorless amorphous solid; $[\alpha]_D^{22} -62.1$ (c 5.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 212 (16200), 248 (12300); IR (KBr) ν_{max} 3432, 2928, 2878, 2858, 1736, 1698, 1252, 1040 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.95 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.44 (1H, ddd, $J = 10.9, 10.3, 5.4$ Hz, H-12), 5.33 (1H, ddd, $J = 10.9, 9.3, 4.6$ Hz, H-13), 5.23 (1H, dd, $J = 9.5, 2.2$ Hz, H-15), 4.36 (1H, ddd, $J = 11.3, 5.6, 2.3$ Hz, H-3), 4.04 (1H, d, $J = 5.6$ Hz, 3-OH), 3.93 (1H, ddd, $J = 9.5, 2.3, 1.4$ Hz, H-7), 3.56 (1H, bd, $J = 2.3$ Hz, 7-OH), 2.70 (1H, dd, $J = 18.0, 1.4$ Hz, H-6a), 2.67 (3H, s, H-21), 2.61 (1H, ddd, $J = 15.3, 9.5, 9.3$ Hz, H-14a), 2.38 (1H, dd, $J = 14.3, 11.3$ Hz, H-2a), 2.36 (1H, dd, $J = 18.0, 9.5$ Hz, H-6b), 2.28 (1H, bd, $J = 15.3$ Hz, H-14b), 2.12 (1H, m, H-11a), 2.06 (1H, dd, $J = 14.3, 2.3$ Hz, H-2b), 2.03 (3H, d, $J = 1.3$ Hz, H-27), 1.96 (1H, m, H-11b), 1.75 (1H, m, H-8), 1.54 (1H, m, H-10a), 1.26 (1H, m, H-9a), 1.25 (3H, s, H-23), 1.17 (1H, m, H-10b), 1.15 (1H, m, H-9b), 1.03 (3H, s, H-22), 0.91 (3H, d, $J = 6.8$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (28), 290 (14), 168 (100), 164 (36), 157 (44), 151 (25); HREIMS m/z 463.2379 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

Epothilone C₄ (21): colorless amorphous solid; $[\alpha]_D^{22}$ -75.6 (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 212 (17200), 248 (12500); IR (KBr) ν_{\max} 3434, 2974, 2932, 2859, 1735, 1686, 1252, 1046 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.96 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 5.26 (1H, dd, J = 9.6, 2.3 Hz, H-15), 4.41 (1H, ddd, J = 11.4, 5.8, 2.5 Hz, H-3), 3.78 (1H, m, H-7), 3.70 (1H, bs, 3-OH), 3.46 (1H, d, J = 0.9 Hz, 7-OH), 3.01 (1H, dq, J = 0.5, 7.0 Hz, H-6), 2.69 (3H, s, H-21), 2.66 (1H, ddd, J = 15.3, 9.6, 8.8 Hz, H-14a), 2.47 (1H, dd, J = 14.5, 11.4 Hz, H-2a), 2.29 (1H, m, H-14b), 2.25 (1H, dd, J = 14.5, 2.5 Hz, H-2b), 2.24 (1H, m, H-11a), 2.07 (3H, d, J = 1.4 Hz, H-27), 1.96 (1H, m, H-11b), 1.51 (2H, m, H-8), 1.44 (2H, m, H-10), 1.37 (2H, m, H-9), 1.32 (3H, s, H-23), 1.17 (3H, d, J = 7.0 Hz, H-24), 1.07 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (7), 276 (15), 171 (33), 168 (100), 164 (23), 151 (22), 111 (13); HREIMS m/z 463.2373 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

Epothilone C₅ (22): colorless amorphous solid; $[\alpha]_D^{22}$ -158.2 (c 0.5, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 205 (19500), 247 (12700); IR (KBr) ν_{\max} 3447, 2972, 2927, 1737, 1690, 1450, 1252, 1181, 986 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.93 (1H, s, H-19), 6.48 (1H, bs, H-17), 5.48 (1H, ddd, J = 10.7, 6.2, 6.2 Hz, H-12), 5.39 (1H, m, H-13), 5.37 (1H, m, H-9), 5.34 (1H, dd, J = 8.0, 2.3 Hz, H-15), 4.29 (1H, dd, J = 6.0, 2.6 Hz, H-7), 4.09 (1H, ddd, J = 10.8, 7.1, 2.9 Hz, H-3), 3.59 (1H, d, J = 7.1 Hz, 3-OH), 3.17 (1H, dq, J = 6.0, 6.9 Hz, H-6), 2.68 (3H, s, H-21), 2.54 (1H, ddd, J = 15.2, 8.1, 8.0 Hz, H-14a), 2.44 (1H, bs, 7-OH), 2.42 (1H, dd, J = 15.1, 2.9 Hz, H-2a), 2.41 (1H, ddd, J = 15.2, 2.3, 2.3 Hz, H-14b), 2.34 (1H, dd, J = 15.1, 10.8 Hz, H-2b), 2.20 (1H, m, H-10a), 2.18 (2H, m, H-11), 2.12 (1H, m, H-10b), 2.06 (3H, bs, H-27), 1.67 (3H, bs, H-25), 1.27 (3H, s, H-23), 1.21 (3H, d, J = 6.9 Hz, H-24), 1.15 (3H, s, H-22); ^{13}C NMR,

see Table 1; EIMS m/z 475 $[M]^+$ (6), 392 (7), 304 (6), 288 (33), 204 (76), 171 (19), 168 (100), 164 (12); HREIMS m/z 475.2380 (calcd. for $C_{26}H_{37}NO_5S$, 475.2392).

Epothilone D₅ (23): colorless amorphous solid; $[\alpha]_D^{22}$ -150 (*c* 0.2, MeOH); UV (MeOH) λ_{max} nm (ϵ) 205 (23300), 248 (13600); IR (KBr) ν_{max} 3439, 2967, 2927, 1736, 1690, 1451, 1254, 1181, 987 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ : 6.94 (1H, s, H-19), 6.51 (1H, bs, H-17), 5.34 (1H, bs, H-9), 5.29 (1H, dd, J = 8.0, 2.4 Hz, H-15), 5.16 (1H, dd, J = 8.2, 6.2 Hz, H-13), 4.30 (1H, bd, J = 4.9 Hz, H-7), 4.19 (1H, ddd, J = 10.8, 7.6, 3.0 Hz, H-3), 3.68 (1H, d, J = 7.6 Hz, 3-OH), 3.17 (1H, dq, J = 4.9, 7.0 Hz, H-6), 2.69 (3H, s, H-21), 2.65 (1H, d, J = 2.1 Hz, 7-OH), 2.56 (1H, ddd, J = 16.2, 8.2, 8.0 Hz, H-14a), 2.40 (1H, dd, J = 15.0, 3.0 Hz, H-2a), 2.39 (1H, bd, J = 16.2 Hz, H-14b), 2.34 (1H, dd, J = 15.0, 10.8 Hz, H-2b), 2.25 (2H, m, H-10a and H-11a), 2.20 (1H, m, H-10b), 2.17 (1H, m, H-11b), 2.05 (3H, d, J = 1.0 Hz, H-27), 1.69 (3H, bs, H-25), 1.68 (3H, bs, H-26), 1.29 (3H, s, H-23), 1.23 (3H, d, J = 7.0 Hz, H-24), 1.16 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 489 $[M]^+$ (4), 406 (4), 338 (7), 302 (13), 218 (35), 171 (10), 168 (100), 153 (20), 125 (10); HREIMS m/z 489.2536 (calcd. for $C_{27}H_{39}NO_5S$, 489.2549).

Epothilone C₆ (24): colorless amorphous solid; $[\alpha]_D^{22}$ -205.2 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 218 (24600), 237 (28800); IR (KBr) ν_{max} 3435, 2967, 2927, 2882, 1732, 1688, 1465, 1258, 988 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ : 6.97 (1H, s, H-19), 6.58 (1H, bs, H-17), 6.43 (1H, dd, 15.5, 10.8 Hz, H-11), 6.11 (1H, dd, J = 10.8, 10.6 Hz, H-12), 5.75 (1H, ddd, J = 15.5, 8.3, 5.6 Hz, H-10), 5.34 (1H, m, H-13), 5.34 (1H, dd, J = 9.7, 2.4 Hz, H-15), 4.16 (1H, ddd, J = 9.2, 4.9, 4.3 Hz, H-3), 3.74 (1H, ddd, J = 2.2, 2.1, 1.7 Hz, H-7), 3.24 (1H, dq, J = 2.1, 6.9 Hz, H-6), 3.06 (1H, d, J = 2.2 Hz, 7-OH), 2.93 (1H, d, J = 4.9 Hz, 3-OH), 2.78 (1H, dddd,

$J = 14.1, 9.9, 9.7, 0.7$, H-14a), 2.71 (3H, s, H-21), 2.48 (1H, m, H-9a), 2.47 (1H, dd, $J = 15.5$, 9.2 Hz, H-2a), 2.40 (1H, dd, $J = 15.5$, 4.3 Hz, H-2b), 2.38 (1H, bdd, $J = 14.1$, 7.8 Hz, H-14b), 2.11 (3H, d, $J = 1.3$ Hz, H-27), 1.96 (1H, m, H-8), 1.33 (3H, s, H-23), 1.11 (3H, d, $J = 6.9$ Hz, H-24), 1.06 (3H, s, H-22), 1.05 (3H, d, $J = 6.8$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 475 $[\text{M}]^+$ (13), 387 (2), 316 (4), 288 (15), 230 (16), 204 (9), 171 (18), 168 (100), 164 (14), 151 (17); HREIMS m/z 475.2361 (calcd. for $\text{C}_{26}\text{H}_{37}\text{NO}_5\text{S}$, 475.2392).

Epithilone C₇ (25): colorless amorphous solid; $[\alpha]_D^{25} -\text{XXX}$ (c 2.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) XXX (XXX), XXX (XXX); IR (KBr) ν_{max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.01 (1H, s, H-19), 6.66 (1H, bs, H-17), 5.59 (1H, ddd, $J = 11.1, 11.1, 3.8$ Hz, H-12), 5.40 (1H, dd, $J = 11.1, 9.2$, H-13), 5.03 (1H, d, $J = 9.3$ Hz, H-15), 4.62 (1H, dd, $J = 9.3, 9.2$ Hz, H-14), 4.18 (1H, bd, $J = 11.0$ Hz, H-3), 3.72 (1H, bs, H-7), 3.20 (1H, bs, 3-OH), 3.09 (1H, dq, $J = 1.9, 6.8$ Hz, H-6), 3.00 (1H, bs, 7-OH), 2.69 (3H, s, H-21), 2.47 (1H, dd, $J = 14.8, 11.0$ Hz, H-2a), 2.32 (1H, dd, $J = 14.8, 2.6$ Hz, H-2b), 2.27 (1H, m, H-11a), 2.19 (3H, bs, H-27), 2.13 (1H, m, H-11b), 1.76 (1H, m, H-8), 1.70 (1H, m, H-10a), 1.35 (1H, m, H-9a), 1.32 (3H, s, H-23), 1.23 (1H, m, H-9b), 1.21 (1H, m, H-10b), 1.18 (3H, d, $J = 6.8$ Hz, H-24), 1.08 (3H, s, H-22), 1.00 (3H, d, $J = 6.9$ Hz, H-25); EIMS m/z 493 $[\text{M}]^+$ XXX; HREIMS m/z 493.XXX (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_6\text{S}$, 493.2498).

Epithilone C₈ (26): colorless amorphous solid; $[\alpha]_D^{25} -75.2$ (c 2.5, MeOH); UV (MeOH) λ_{max} nm (ϵ) 210 (16800), 248 (17800); IR (KBr) ν_{max} 3443, 2932, 2881, 1734, 1689, 1465, 1255, 1183, 976 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.93 (1H, s, H-19), 6.62 (1H, dd, $J = 15.6, 0.6$ Hz, H-17), 6.49 (1H, dd, $J = 15.6, 6.6$ Hz, H-16), 5.52 (1H, dddd, $J = 9.5, 6.6, 2.8, 0.6$ Hz, H-

15), 5.42 (1H, m, H-12), 5.41 (1H, m, H-13), 4.13 (1H, ddd, $J = 11.0, 5.3, 2.8$ Hz, H-3), 3.69 (1H, ddd, $J = 3.7, 2.8, 2.5$ Hz, H-7), 3.11 (1H, dq, $J = 2.5, 6.8$ Hz, H-6), 2.95 (1H, d, $J = 5.3$ Hz, 3-OH), 2.90 (1H, d, $J = 2.8$ Hz, 7-OH), 2.69 (3H, s, H-21), 2.67 (1H, ddd, $J = 14.9, 9.5, 8.4$ Hz, H-14a), 2.48 (1H, dd, $J = 15.6, 11.0$ Hz, H-2a), 2.33 (1H, dd, $J = 15.6, 2.8$ Hz, H-2b), 2.30 (1H, bd, $J = 14.9$ Hz, H-14b), 2.14 (1H, m, H-11a), 2.03 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.31 (1H, m, H-9a), 1.29 (3H, s, H-23), 1.17 (3H, d, $J = 6.8$ Hz, H-24), 1.16 (1H, m, H-10b), 1.14 (1H, m, H-9b), 1.05 (3H, s, H-22), 0.97 (3H, d, $J = 7.1$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (21), 310 (10), 276 (21), 171 (83), 154 (100), 150 (27), 111 (18); HREIMS m/z 463.2382 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

Epothilone C₉ (27): colorless amorphous solid; $[\alpha]_D^{25} -93.4$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 209 (15200), 254 (15700); IR (KBr) ν_{max} 3416, 2966, 2932, 1736, 1689, 1463, 1249, 1011 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.06 (1H, s, H-19), 6.65 (1H, bs, H-17), 6.56 (1H, dd, $J = 10.6, 4.4$ Hz, 27-OH), 5.55 (1H, d, $J = 6.2$ Hz, 3-OH), 5.52 (1H, dd, $J = 11.6, 2.0$ Hz, H-15), 5.44 (1H, dddd, $J = 11.2, 10.7, 3.1, 1.7$ Hz, H-12), 5.35 (1H, dddd, $J = 11.0, 10.7, 3.9, 1.7$ Hz, H-13), 4.47 (1H, ddd, $J = 12.5, 4.4, 1.3$ Hz, H-27a), 4.35 (1H, ddd, $J = 11.7, 6.2, 2.6$ Hz, H-3), 4.20 (1H, ddd, $J = 12.5, 10.6, 0.9$ Hz, H-27b), 3.63 (1H, ddd, $J = 4.6, 1.8, 0.9$ Hz, H-7), 3.24 (1H, d, $J = 1.8$ Hz, 7-OH), 3.13 (1H, dq, $J = 0.9, 6.8$ Hz, H-6), 2.80 (1H, ddd, $J = 14.8, 11.6, 11.0$ Hz, H-14a), 2.71 (3H, s, H-21), 2.40 (1H, dd, $J = 14.4, 11.7$ Hz, H-2a), 2.24 (1H, m, H-11a), 2.06 (1H, dd, $J = 14.4, 2.6$ Hz, H-2b), 2.01 (1H, ddd, $J = 14.8, 3.9, 2.0$ Hz, H-14b), 2.00 (1H, m, H-11b), 1.77 (1H, m, H-8), 1.69 (1H, m, H-10a), 1.35 (1H, m, H-9a), 1.35 (3H, s, H-23), 1.19 (1H, m, H-10b), 1.19 (3H, d, $J = 6.8$ Hz, H-24), 1.18 (1H, m, H-9b), 1.01 (3H, d, $J =$

7.1 Hz, H-25), 0.98 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 493 $[\text{M}]^+$ (17), 306 (64), 184 (50), 171 (30), 167 (38), 166 (100), 138 (12); HREIMS m/z 493.2502 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_6\text{S}$, 493.2498).

trans-Epothilone C₁ (28): colorless amorphous solid; $[\alpha]_D^{22}$ -84 (*c* 0.2, MeOH); UV (MeOH) λ_{max} nm (ϵ) 211 (17400), 248 (12900); IR (KBr) ν_{max} 3433, 2961, 2933, 2879, 1730, 1708, 1457, 1251, 975 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 7.00 (1H, s, H-19), 6.64 (1H, bs, H-17), 5.45 (1H, ddd, J = 15.2, 6.5, 6.5 Hz, H-12), 5.42 (1H, dd, J = 6.4, 3.7 Hz, H-15), 5.35 (1H, dt, J = 15.2, 7.1 Hz, H-13), 4.42 (1H, m, H-3), 3.58 (1H, ddd, J = 8.1, 7.9, 2.8 Hz, H-7), 3.24 (1H, m, H-6), 3.14 (1H, dq, J = 4.0, 6.9 Hz, H-6), 2.92 (1H, d, J = 7.9 Hz, 7-OH), 2.71 (3H, s, H-21), 2.71 (2H, m, H-2), 2.53 (2H, m, H-14), 2.17 (1H, d, J = 2.17 Hz, 3-OH), 2.11 (1H, m, H-11a), 2.06 (3H, bs, H-27), 1.93 (1H, m, H-11b), 1.68 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.33 (1H, m, H-8), 1.26 (3H, d, J = 6.8 Hz, H-24), 1.16 (1H, m, H-10b), 1.12 (3H, d, J = 6.9 Hz, H-22), 1.07 (1H, m, H-9b), 1.00 (3H, d, J = 6.8 Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (6), 290 (21), 289 (20), 204 (23), 194 (19), 190 (22), 168 (100), 164 (48), 157 (14), 152 (19), 151 (17), 139 (15), 111 (18); HREIMS m/z 463.2371 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

trans-Epothilone C₂ (29): colorless amorphous solid; $[\alpha]_D^{22}$ -3 (*c* 1.5, MeOH); UV (MeOH) λ_{max} nm (ϵ) 211 (15800), 248 (11900); IR (KBr) ν_{max} 3435, 2963, 2931, 2878, 1731, 1706, 1457, 1273, 979 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 6.99 (1H, s, H-19), 6.57 (1H, bs, H-17), 5.56 (1H, ddd, J = 15.1, 7.4, 7.0 Hz, H-12), 5.41 (1H, ddd, J = 15.1, 7.0, 6.9 Hz, H-13), 5.41 (1H, dd, J = 7.7, 2.8 Hz, H-15), 4.13 (1H, dddd, J = 6.7, 6.2, 5.6, 5.1 Hz, H-3), 3.78 (1H, ddd, J = 8.2, 6.5, 1.9 Hz, H-7), 3.18 (1H, d, J = 5.6 Hz, 3-OH), 3.06 (1H, dq, J = 8.2, 7.1 Hz,

H-6), 2.98 (1H, dq, $J = 6.2, 7.0$ Hz, H-4), 2.71 (3H, s, H-21), 2.64 (1H, dd, $J = 15.1, 6.7$ Hz, H-2a), 2.54 (1H, dd, $J = 15.1, 5.1$ Hz, H-2b), 2.44 (2H, m, H-14), 2.22 (1H, dddd, $J = 13.8, 7.0, 6.2, 2.9$ Hz, H-11a), 2.10 (3H, d, $J = 1.1$ Hz, H-27), 2.09 (1H, d, $J = 6.5$ Hz, 7-OH), 1.88 (1H, dddd, $J = 13.8, 10.9, 7.4, 2.9$ Hz, H-11b), 1.65 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.56 (1H, dddd, $J = 12.7, 12.7, 3.9, 3.9$ Hz, H-9a), 1.20 (3H, d, $J = 7.1$ Hz, H-24), 1.15 (3H, d, $J = 7.0$ Hz, H-23), 1.13 (1H, m, H-10b), 1.04 (1H, m, H-9b), 1.01 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (13), 290 (11), 190 (10), 168 (100), 164 (20), 157 (26), 139 (17); HREIMS m/z 463.2383 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).

Epothilone I₁ (30): colorless amorphous solid; $[\alpha]_D^{25}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{max} nm (ϵ) XXX; IR (KBr) ν_{max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.96 (1H, s, H-19), 6.54 (1H, bs, H-17), 5.49 (1H, ddd, $J = 10.3, 7.3, 7.3$ Hz, H-12), 5.33 (1H, dd, $J = 8.3, 4.4$ Hz, H-15), 5.31 (1H, m, H-13), 4.15 (1H, ddd, $J = 8.0, 5.0, 4.6$ Hz, H-3), 3.80 (1H, m, H-7), 3.21 (1H, dq, $J = 6.0, 6.9$ Hz, H-6), 2.89 (1H, d, $J = 5.0$ Hz, 3-OH), 2.70 (3H, s, H-21), 2.65 (1H, ddd, $J = 15.8, 8.5, 8.3$ Hz, H-14a), 2.42 (2H, m, H-2), 2.35 (1H, m, H-14b), 2.27 (1H, bd, $J = 3.3$ Hz, 7-OH), 2.13 (1H, m, H-11a), 2.09 (3H, d, $J = 1.2$ Hz, H-27), 2.00 (1H, m, H-11b), 1.72 (1H, m, H-8), 1.40 (2H, m, H-10_p), 1.37 (1H, m, H-9_a), 1.36 (2H, m, H-9_a), 1.32 (3H, s, H-23), 1.27 (3H, m, H-9_b and H-10_a), 1.13 (3H, d, $J = 6.9$ Hz, H-24), 1.09 (3H, s, H-22), 0.94 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 75 MHz) δ 221.3 (s, C-5), 171.1 (s, C-1), 164.8 (s, C-20), 152.4 (s, C-18), 137.4 (s, C-16), 133.8 (d, C-12), 124.6 (d, C-13), 120.0 (d, C-17), 116.2 (d, C-19), 78.8 (d, C-15), 74.9 (d, C-7), 74.7 (d, C-3), 51.6 (s, C-4), 43.7 (d, C-6), 38.9 (t, C-2), 34.3 (d, C-8), 31.6 (t, C-14), 29.3 (t, C-9_a), 28.6 (t, C-10_p), 28.2 (t, C-10_a), 26.6 (t, C-

11), 24.8 (t, C-9_β), 23.6 (q, C-22), 19.3 (q, C-23), 19.3 (q, C-21), 16.5 (q, C-25), 15.5 (q, C-27), 13.7 (q, C-24); EIMS m/z 505 [M]⁺ XXX; HREIMS m/z 505.XXX (calcd. for C₂₈H₄₃NO₅S, 505.XXX).

Epothilone I₂ (31): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.95 (1H, s, H-19), 6.53 (1H, bs, H-17), 5.40 (1H, m, H-12), 5.38 (1H, dd, J = 9.8, 3.3 Hz, H-15), 5.37 (1H, m, H-13), 4.21 (1H, ddd, J = 8.6, 3.8, 3.6 Hz, H-3), 3.85 (1H, ddd, J = 8.5, 5.8, 2.2 Hz, H-7), 3.18 (1H, dq, J = 8.5, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.65 (1H, ddd, J = 15.2, 9.8, 9.0 Hz, H-14a), 2.51 (1H, d, J = 3.6 Hz, 3-OH), 2.37 (2H, m, H-2), 2.32 (1H, bd, J = 15.2 Hz, H-14b), 2.09 (3H, d, J = 1.3 Hz, H-27), 2.07 (2H, m, H-11), 1.78 (1H, m, H-8), 1.65 (1H, d, J = 5.8 Hz, 7-OH), 1.57 (1H, m, H-10_βa), 1.44 (1H, m, H-10_αa), 1.42 (1H, m, H-9_β), 1.32 (3H, s, H-23), 1.21 (1H, m, H-10_βb), 1.17 (3H, d, J = 7.0 Hz, H-24), 1.13 (2H, m, H-9_α), 1.06 (3H, s, H-22), 0.95 (3H, d, J = 7.0 Hz, H-25_α), 0.91 (3H, d, J = 6.5 Hz, H-25_β), 0.68 (1H, m, H-10_αb); ¹³C NMR (CDCl₃, 100 MHz) δ 220.4 (s, C-5), 171.3 (s, C-1), XXX (s, C-20), 152.4 (s, C-18), 137.6 (s, C-16), 134.5 (d, C-12), 125.3 (d, C-13), 119.6 (d, C-17), 116.2 (d, C-19), 78.6 (d, C-15), 77.2 (d, C-7), 75.0 (d, C-3), 51.0 (s, C-4), 44.6 (d, C-6), 38.2 (t, C-2), 36.9 (t, C-9_α), 34.5 (t, C-10_α), 32.6 (d, C-8), 32.0 (t, C-14), 30.0 (d, C-9_β), 27.4 (t, C-11), 26.6 (t, C-10_β), 25.0 (q, C-22), 21.5 (q, C-25_β), 19.3 (q, C-21), 17.9 (q, C-25_α), 17.7 (q, C-23), 15.8 (q, C-24), 15.6 (q, C-27); EIMS m/z 519 [M]⁺ XXX; HREIMS m/z 519.XXX (calcd. for C₂₉H₄₅NO₅S, 519.XXX).

Epothilone I₃ (32): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.95 (1H,

s, H-19), 6.52 (1H, bs, H-17), 5.32 (1H, dd, $J = 9.1, 3.0$ Hz, H-15), 5.08 (1H, dd, $J = 8.5, 3.9$ Hz, H-13), 4.13 (1H, ddd, $J = 9.4, 4.3, 3.2$ Hz, H-3), 3.81 (1H, m, H-7), 3.18 (1H, dq, $J = 6.8, 7.0$ Hz, H-6), 2.83 (1H, d, $J = 4.3$ Hz, 3-OH), 2.70 (3H, s, H-21), 2.61 (1H, ddd, $J = 15.8, 9.1, 8.5$ Hz, H-14a), 2.43 (1H, dd, $J = 14.0, 3.2$ Hz, H-2a), 2.38 (2H, dd, $J = 14.0, 9.4$ Hz, H-2b), 2.30 (1H, bd, $J = 15.8$ Hz, H-14b), 2.16 (1H, ddd, $J = 14.1, 8.3, 7.4$ Hz, H-11a), 2.08 (3H, d, $J = 1.0$ Hz, H-27), 1.99 (1H, d, $J = 4.7$ Hz, 7-OH), 1.92 (1H, ddd, $J = 14.1, 6.3, 6.3$ Hz, H-11b), 1.82 (1H, m, H-8), 1.67 (3H, s, H-26), 1.51 (1H, m, H-10_a), 1.40 (1H, m, H-9_b), 1.33 (1H, m, H-10_b), 1.31 (3H, s, H-23), 1.27 (1H, m, H-10_a), 1.23 (1H, m, H-9_a), 1.16 (3H, d, $J = 7.0$ Hz, H-24), 1.10 (1H, m, H-9_b), 1.07 (3H, s, H-22), 0.95 (3H, d, $J = 7.0$ Hz, H-25_a), 0.92 (3H, d, $J = 6.5$ Hz, H-25_b), 0.75 (1H, m, H-10_b); EIMS m/z 533 [M]⁺ XXX; HREIMS m/z 533.XXX (calcd. for C₃₀H₄₇NO₅S, 533.XXX).

Epothilone I₄ (33): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{max} nm (ϵ) XXX; IR (KBr) ν_{max} XXX cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.95 (1H, s, H-19), 6.53 (1H, bs, H-17), 5.47 (1H, dt, $J = 11.1, 5.8$ Hz, H-12), 5.33 (1H, ddd, $J = 9.2, 3.9, 0.5$ Hz, H-15), 5.33 (1H, m, H-13), 4.09 (1H, dddd, $J = 9.6, 8.1, 4.5, 3.3$ Hz, H-3), 3.83 (1H, m, H-7), 3.57 (1H, bs, 3-OH), 2.89 (1H, dq, $J = 7.4, 7.1$ Hz, H-6), 2.83 (1H, dq, $J = 8.1, 7.1$ Hz, H-4), 2.70 (3H, s, H-21), 2.64 (1H, m, H-14a), 2.42 (1H, dd, $J = 14.2, 3.3$ Hz, H-2a), 2.43 (1H, dd, $J = 14.2, 9.6$ Hz, H-2b), 2.30 (1H, m, H-14b), 2.10 (3H, d, $J = 1.3$ Hz, H-27), 2.09 (2H, m, H-11), 1.81 (1H, m, H-8), 1.74 (1H, bd, $J = 5.6$ Hz, 7-OH), 1.53 (1H, m, H-10_a), 1.49 (1H, m, H-9_b), 1.47 (1H, m, H-10_a), 1.27 (1H, m, H-10_b), 1.24 (1H, m, H-9_a), 1.17 (3H, d, $J = 7.1$ Hz, H-23), 1.14 (1H, m, H-9_b), 1.08 (3H, d, $J = 7.1$ Hz, H-24), 0.97 (3H, d, $J = 6.9$ Hz, H-25_a),

0.91 (3H, d, $J = 6.5$ Hz, H-25_p), 0.79 (1H, m, H-10_ab); ^{13}C NMR (CDCl_3 , 100 MHz) δ 217.0 (s, C-5), 170.8 (s, C-1), 164.8 (s, C-20), 152.4 (s, C-18), 137.1 (s, C-16), 134.6 (d, C-12), 124.7 (d, C-13), 120.2 (d, C-17), 116.4 (d, C-19), 78.7 (d, C-15), 76.4 (d, C-7), 71.3 (d, C-3), 50.7 (d, C-4), 50.1 (d, C-6), 40.7 (t, C-2), 38.5 (t, C-9_w), 35.5 (t, C-10_w), 33.4 (d, C-8), 31.8 (t, C-14), 30.0 (d, C-9_p), 27.2 (t, C-11), 26.7 (t, C-10_p), 21.4 (q, C-25_p), 19.3 (q, C-21), 18.2 (q, C-25_w), 15.4 (q, C-27), 14.4 (q, C-24), 13.1 (q, C-23); EIMS m/z 505 $[\text{M}]^+$ XXX; HREIMS m/z 505.XXX (calcd. for $\text{C}_{28}\text{H}_{43}\text{NO}_5\text{S}$, 505.XXX).

Epothilone I₅ (34): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{max} nm (ϵ) XXX; IR (KBr) ν_{max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.97 (1H, s, H-19), 6.52 (1H, bs, H-17), 5.32 (1H, dd, $J = 7.1, 6.2$ Hz, H-15), 5.03 (1H, dd, $J = 8.4, 5.0$ Hz, H-13), 4.05 (1H, dddd, $J = 7.5, 7.2, 5.9, 4.6$ Hz, H-3), 3.91 (1H, m, H-7), 3.17 (1H, d, $J = 5.9$ Hz, 3-OH), 2.94 (1H, dq, $J = 7.2, 7.1$ Hz, H-4), 2.87 (1H, dq, $J = 6.5, 6.9$ Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, $J = 14.6, 4.6$ Hz, H-2a), 2.60 (1H, m, H-14a), 2.53 (1H, dd, $J = 14.6, 7.5$ Hz, H-2b), 2.31 (1H, m, H-14b), 2.10 (3H, d, $J = 1.1$ Hz, H-27), 2.10 (1H, m, H-11a), 2.02 (1H, m, H-11b), 1.97 (1H, bd, $J = 5.6$ Hz, 7-OH), 1.84 (1H, m, H-8), 1.66 (3H, s, H-26), 1.55 (1H, m, H-9_p), 1.49 (1H, m, H-10_pa), 1.39 (1H, m, H-10_pb), 1.33 (1H, m, H-10_a), 1.31 (1H, m, H-9_aa), 1.15 (3H, d, $J = 7.1$ Hz, H-23), 1.12 (1H, m, H-9_ab), 1.11 (3H, d, $J = 6.9$ Hz, H-24), 0.97 (3H, d, $J = 6.9$ Hz, H-25_w), 0.94 (1H, m, H-10_ab), 0.93 (3H, d, $J = 6.6$ Hz, H-25_p); EIMS m/z 519 $[\text{M}]^+$ XXX; HREIMS m/z 519.XXX (calcd. for $\text{C}_{29}\text{H}_{45}\text{NO}_5\text{S}$, 519.XXX).

Epothilone I₆ (35): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{max} nm (ϵ) XXX; IR (KBr) ν_{max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.97 (1H,

s, H-19), 6.52 (1H, bs, H-17), 5.24 (1H, dd, $J = 6.9, 6.9$ Hz, H-15), 5.02 (1H, dd, $J = 8.8, 5.2$ Hz, H-13), 4.22 (1H, tdd, $J = 6.1, 5.6, 4.8$ Hz, H-3), 3.76 (1H, ddd, $J = 6.1, 5.7, 5.6$ Hz, H-7), 3.13 (1H, d, $J = 5.6$ Hz, 3-OH), 3.05 (1H, dq, $J = 4.8, 7.0$ Hz, H-4), 2.79 (1H, dq, $J = 5.6, 6.9$ Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, m, H-14a), 2.57 (2H, d, $J = 6.1$ Hz, H-2a), 2.30 (1H, m, H-14b), 2.08 (3H, d, $J = 1.0$ Hz, H-27), 2.02 (2H, m, H-11), 1.73 (1H, d, $J = 6.1$ Hz, 7-OH), 1.69 (1H, m, H-8), 1.66 (3H, s, H-26), XXX (H-9_a, H-9_b, H-10_a, H-10_b), 1.21 (3H, d, $J = 7.0$ Hz, H-22), 1.16 (3H, d, $J = 6.9$ Hz, H-24), 0.94 (3H, d, $J = 6.9$ Hz, H-25_a), 0.91 (3H, d, $J = 6.4$ Hz, H-25_b); EIMS m/z 519 [M]⁺ XXX; HREIMS m/z 519.XXX (calcd. for C₂₉H₄₅NO₅S, 519.XXX).

Epothilone K (36): colorless amorphous solid; $[\alpha]_D^{22} -7$ (c 0.08, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 212 (16700), 248 (12500); IR (KBr) ν_{\max} 3431, 2963, 2927, 2856, 1731, 1712, 1262, 1093, 1021, 802 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.95 (1H, s, H-19), 6.51 (1H, bs, H-17), 5.49 (3H, m, H-15, H-13, and H-12), 4.04 (1H, dddd, $J = 7.9, 7.6, 6.9, 3.3$ Hz, H-3), 3.36 (1H, dq, $J = 6.9, 6.8$ Hz, H-6), 2.83 (1H, d, $J = 7.6$ Hz, 3-OH), 2.75 (1H, ddd, $J = 16.1, 6.6, 3.4$ Hz, H-14a), 2.74 (1H, dd, $J = 15.3, 3.3$ Hz, H-2a), 2.71 (3H, s, H-21), 2.58 (2H, m, H-14b and H-8), 2.50 (1H, dd, $J = 15.3, 7.9$ Hz, H-2b), 2.29 (1H, m, H-11a), 2.10 (1H, m, H-11b), 2.09 (3H, d, $J = 0.7$ Hz, H-27), 1.78 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.48 (1H, m, H-10b), 1.18 (1H, m, H-9b), 1.15 (3H, d, $J = 6.8$ Hz, H-22), 1.03 (3H, d, $J = 6.5$ Hz, H-25); EIMS m/z 405 [M]⁺ (38), 317 (12), 260 (9), 232 (10), 204 (14), 190 (16), 168 (100), 164 (30), 151 (28); HREIMS m/z 405.XXX (calcd. for C₂₆H₃₉NO₅S, 405.XXX).

(37): colorless amorphous solid; $[\alpha]_D^{22} -27.5$ (c 0.4, MeOH); UV (MeOH) λ_{\max} nm (ϵ).

211 (16100), 247 (12100); IR (KBr) ν_{\max} 3431, 2967, 2929, 2875, 1704, 1462, 1381, 1010 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.94 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.56 (1H, dtt, $J = 10.8$, 7.3, 1.4 Hz, H-12), 5.39 (1H, dtt, $J = 10.8$, 7.3, 1.4 Hz, H-13), 4.17 (1H, t, $J = 6.6$ Hz, H-15), 3.50 (1H, ddd, $J = 8.7$, 2.6, 2.6 Hz, H-7), 3.10 (1H, d, $J = 2.6$, 7-OH), 2.90 (1H, dq, $J = 2.6$, 7.2 Hz, H-6), 2.77 (1H, sep, $J = 6.9$ Hz, H-4), 2.70 (3H, s, H-21), 2.40 (2H, m, H-14), 2.07 (2H, m, H-11), 2.04 (3H, d, $J = 1.1$ Hz, H-27), 1.78 (1H, bs, 15-OH), 1.74 (1H, m, H-9a), 1.50 (1H, m, H-8), 1.46 (1H, m, H-10a), 1.27 (1H, m, H-10b), 1.11 (1H, m, H-9b), 1.094 (3H, d, $J = 6.9$ Hz, H-23), 1.089 (3H, d, $J = 6.9$ Hz, H-22), 1.08 (3H, d, $J = 7.2$ Hz, H-24), 0.82 (3H, d, $J = 6.7$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.5 (s, C-5), 164.6 (s, C-20), 152.9 (s, C-18), 141.5 (s, C-16), 133.4 (d, C-12), 125.0 (d, C-13), 119.2 (d, C-17), 115.6 (d, C-19), 77.2 (d, C-15), 74.9 (d, C-7), 44.9 (d, C-6), 40.0 (d, C-4), 35.5 (d, C-8), 33.5 (t, C-14), 32.3 (t, C-9), 27.9 (t, C-11), 26.9 (t, C-10), 19.2 (q, C-21), 18.6 (q, C-23), 18.1 (q, C-22), 15.6 (q, C-25), 14.4 (q, C-27), 9.3 (q, C-24); EIMS m/z 407 $[\text{M}]^+$ (0.1), 204 (0.8), 168 (100), 140 (3.4); HREIMS m/z 407.XXX (calcd. for $\text{C}_{23}\text{H}_{37}\text{NO}_5\text{S}$, 407.XXX).

(38): colorless amorphous solid; $[\alpha]_D^{25} +25.0$ (c 0.5, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 212 (17700), 247 (13400); IR (KBr) ν_{\max} 3427, 2971, 2933, 2878, 2858, 1709, 1457, 1377, 1186, 1023 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.95 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.52 (1H, dtt, $J = 10.9$, 7.2, 1.4 Hz, H-12), 5.39 (1H, dtt, $J = 10.9$, 7.1, 1.2 Hz, H-13), 4.18 (1H, ddt, $J = 3.4$, 0.4, 6.7 Hz, H-15), 2.71 (3H, s, H-21), 2.51 (1H, bq, $J = 6.8$ Hz, H-8), 2.48 (1H, dq, $J = 17.7$, 7.4 Hz, H-6a), 2.41 (1H, dq, $J = 17.7$, 7.2 Hz, H-6b), 2.39 (2H, ddd, $J = 7.1$, 6.7, 1.4 Hz, H-14), 2.06 (2H, ddt, 7.2, 1.2, 7.0 Hz, H-11), 2.05 (3H, d, $J = 1.4$ Hz, H-27), 1.81 (1H, d, $J = 3.4$ Hz,

15-OH), 1.66 (1H, m, H-9a), 1.32 (1H, m, H-9b), 1.31 (2H, m, H-10), 1.06 (3H, d, $J = 6.9$ Hz, H-25), 1.04 (3H, dd, $J = 7.4, 7.2$ Hz, H-24); ^{13}C NMR (CDCl_3 , 75 MHz) δ 215.3 (s, C-7), 164.6 (s, C-20), 152.9 (s, C-18), 141.5 (s, C-16), 132.7 (d, C-12), 125.3 (d, C-13), 119.2 (d, C-17), 115.6 (d, C-19), 77.2 (d, C-15), 46.0 (d, C-8), 34.3 (t, C-14), 33.5 (t, C-6), 32.7 (t, C-9), 27.5 (t, C-11), 27.3 (t, C-10), 19.2 (q, C-21), 16.5 (q, C-25), 14.4 (q, C-27), 7.8 (q, C-24); EIMS m/z 335 [M] $^+$ (2), 317 (4), 170 (27), 169 (67), 168 (100), 140 (20); HREIMS m/z 335.1912 (calcd. for $\text{C}_{19}\text{H}_{29}\text{NO}_2\text{S}$, 335.1919).

(39): colorless amorphous solid; $[\alpha]_D^{22} +26.4$ (c 0.27, MeOH); UV (MeOH) λ_{max} nm (ϵ) 203 (19100), 244 (12500); IR (KBr) ν_{max} 3430, 2970, 2934, 2877, 1710, 1458, 1377, 1184 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.94 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.17 (1H, t, $J = 7.3$ Hz, H-13), 4.13 (1H, m, H-15), 2.70 (3H, s, H-21), 2.51 (1H, bq, $J = 6.8$ Hz, H-8), 2.47 (1H, dq, $J = 17.7, 7.2$ Hz, H-6a), 2.41 (1H, dq, $J = 17.7, 7.2$ Hz, H-6b), 2.33 (2H, bdd, $J = 7.3, 6.8$ Hz, H-14), 2.05 (3H, d, $J = 1.2$ Hz, H-27), 2.03 (2H, m, H-11), 1.71 (1H, d, $J = 3.2$ Hz, 15-OH), 1.69 (3H, d, $J = 1.3$ Hz, H-26), 1.62 (1H, m, H-9a), 1.32 (3H, m, H-10 and H-9b), 1.06 (3H, d, $J = 6.9$ Hz, H-25), 1.03 (3H, t, $J = 7.2$ Hz, H-24); EIMS m/z 349 [M] $^+$ (0.7), 331 (1.7), 168 (100), 140 (5.1); HREIMS m/z 349.XXX (calcd. for $\text{C}_{20}\text{H}_{31}\text{NO}_2\text{S}$, 349.XXX).

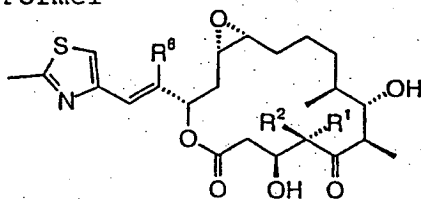
Tab 1. Aktivität von Epothilonen und Verbindungen (1) bis (39) gegen Maus-Fibroblasten (L929, IC50 /ng/ml/)

Struktur- typ	Epothilone				
	A _r	B _r	C _r	D _r	trans C _r
Ausgangs- epothilon	(1) 4	(2) 1-2	(14) 50-100	(15) 20	-
21-Hydroxy (E&F)	(3) 10	(4) 1.5	-	-	-
Oxazoles (G&H)	(10) 6	(11) 1	(12) 120	(13) 11	-
(R)-4-Desmethyl (X ₁)	(5) 20	-	(16) 200	(17) 20	(28) 400
(S)-4-Desmethyl (X ₂)	(6) 7	-	(18) 25-30	(19) 12	(29) 80
6-Desmethyl (X ₃)	-	-	(20) 1500	-	-
8-Desmethyl (X ₄)	-	-	(21) 800	-	-
8,9-Dehydro (X ₅)	-	-	(22) 1500	(23) 200	-
10,11-Dehydro (X ₆)	-	-	(24) 120	-	-
14-Hydroxy (X ₇)	-	-	(25)	-	-
16-Desmethyl (X ₈)	(7) 20	-	(26) 250	-	-
27-Hydroxy (X ₉)	(8) 100	-	(27) 200	-	-
21-Methyl (X ₁₀)	-	(9) 1.5	-	-	-
Verbindung	-	-	(36) 180	-	-
Verbindung	-	-	(37) 50	-	-
Verbindung	-	-	(38) 2000	(39) 500	-

Epothilon-Nebenkomponenten

Patentansprüche

1. Epothilon der Formel



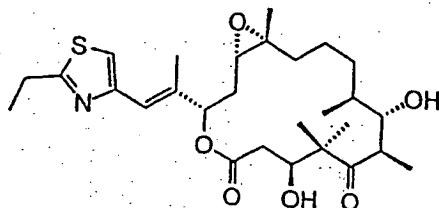
Epothilone A₁ (5) R¹ = H; R², R⁸ = Me

Epothilone A₂ (6) R² = H; R¹, R⁸ = Me

Epothilone A₈ (7) R⁸ = H; R¹, R² = Me oder

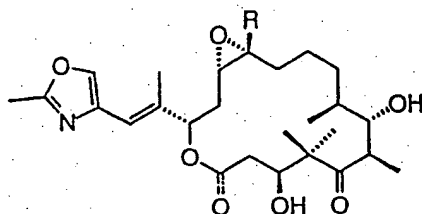
Epothilone A₉ (8) R¹ = CH₂OH; R², R⁸ = Me

2. Epothilon der Formel



Epothilone B₁₀ (9)

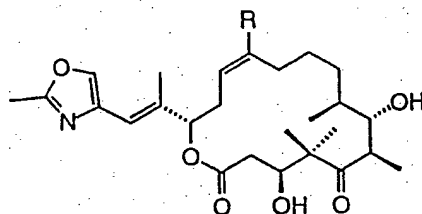
3. Epothilon der Formel

✓ Epothilone G₁ (10) R = H

oder

✓ Epothilone G₂ (11) R = Me

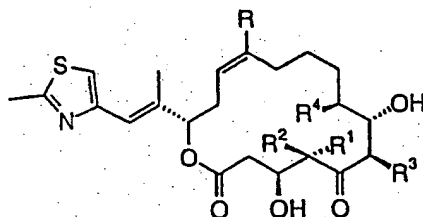
4. Epothilon der Formel

✓ Epothilone H₁ (12) R = H

oder

✓ Epothilone H₂ (13) R = Me

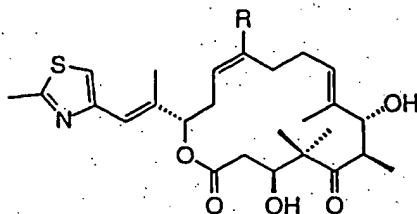
5. Epothilon der Formel

✓ Epothilone C₁ (16) R¹ = H; R², R³, R⁴ = Me; R = H✓ Epothilone D₁ (17) R¹ = H; R², R³, R⁴ = Me; R = Me✓ Epothilone C₂ (18) R² = H; R¹, R³, R⁴ = Me; R = H✓ Epothilone D₂ (19) R² = H; R¹, R³, R⁴ = Me; R = Me✓ Epothilone C₃ (20) R³ = H; R¹, R², R⁴ = Me; R = H

oder

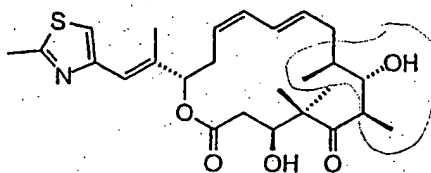
✓ Epothilone C₄ (21) R⁴ = H; R¹, R², R³ = Me; R = H

6. Epothilon der Formel

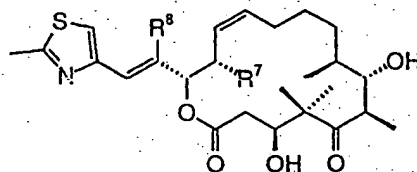
Epothilone C₅ (22) R = HEpothilone D₅ (23) R = Me

oder

7. Epothilon der Formel

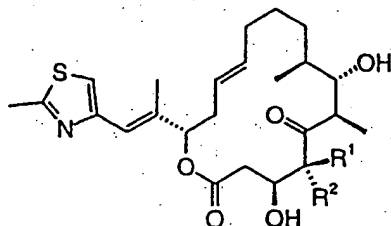
✓ Epothilone C₆ (24)

8. Epothilin der Formel

✓ Epothilone C₇ (25) R⁷ = OH; R⁸ = Me✓ Epothilone C₈ (26) R⁸, R⁷ = H✓ Epothilone C₉ (27) R⁸ = CH₂OH; R⁷ = H

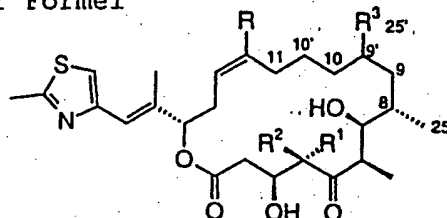
oder

9. Epothilon der Formel

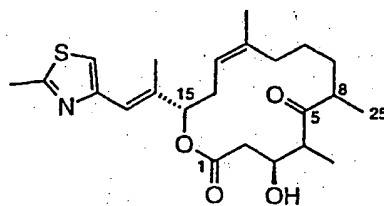
✓ trans-Epothilone C₁ (28) R¹ = H; R² = Me✓ trans-Epothilone C₂ (29) R² = H; R¹ = Me

oder

10. Epothilon der Formel

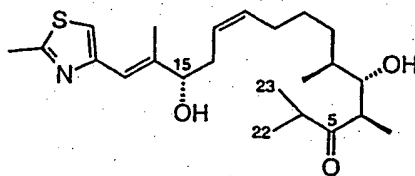
Epothilone I₁ (30) R, R³ = H; R¹, R² = MeEpothilone I₂ (31) R = H; R¹, R², R³ = MeEpothilone I₃ (32) R¹, R², R³, R = MeEpothilone I₄ (33) R², R = H; R¹, R³ = MeEpothilone I₅ (34) R² = H; R¹, R³, R = Me oderEpothilone I₆ (35) R¹ = H; R², R³, R = Me

11. Epothilon der Formel



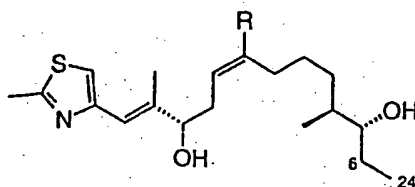
✓ Epothilone K (36)

12. Verbindung der Formel



(37)

13. Verbindung der Formel



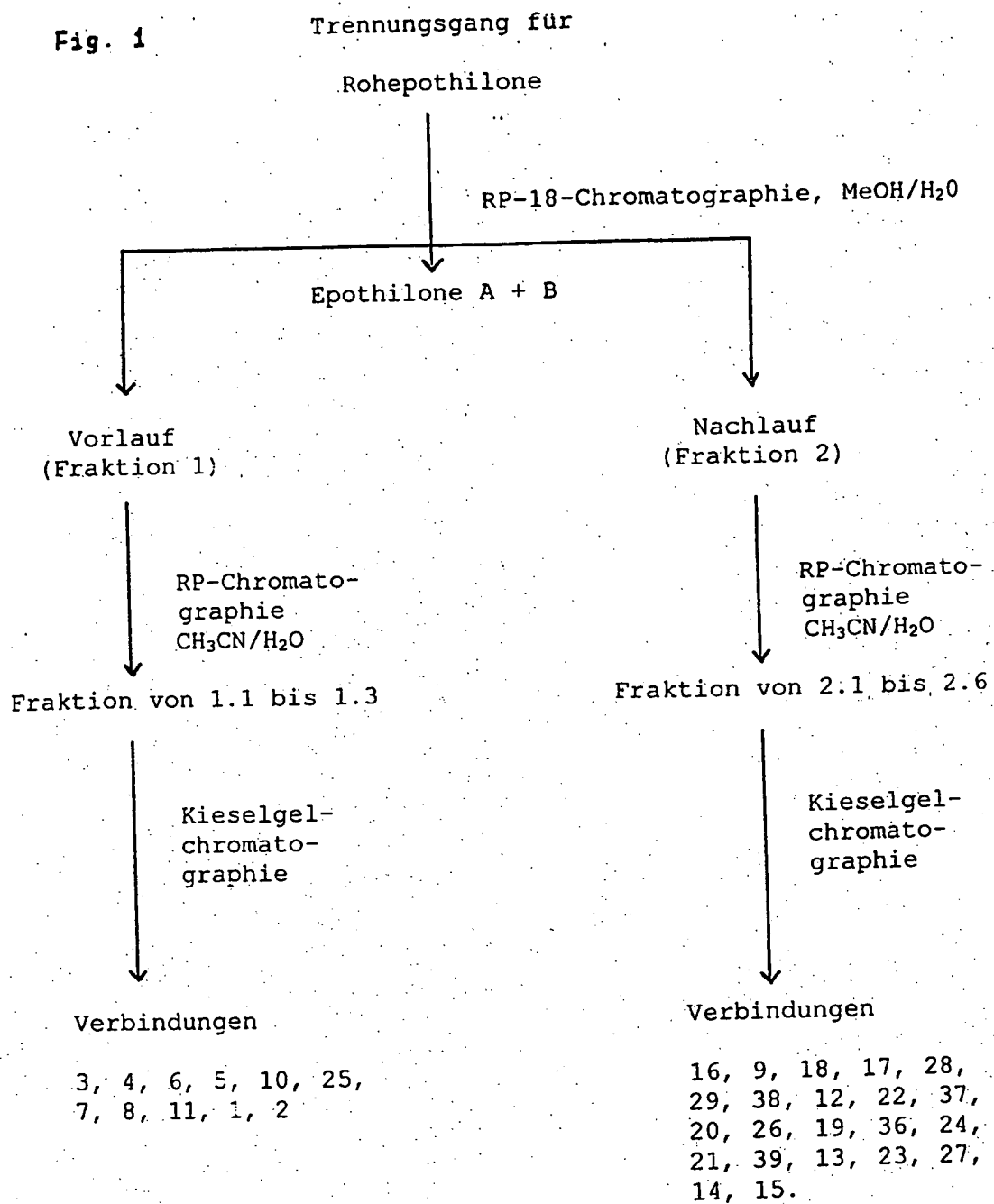
(38) R = H

(39) R = Me
32

oder

1/2

Fig. 1



2/2

Fig. 2

fraction 1	1.1	Epothilone E (3)	variable ^a
		Epothilone F (4)	variable ^a
		Epothilone A ₂ (6)	14.5 mg
		Epothilone A ₁ (5)	3.1 mg
		Epothilone G ₁ (10)	62.3 mg
	1.2	Epothilone C ₇ (25)	0.9 mg
		Epothilone A ₈ (7)	38.7 mg
	1.3	Epothilone A ₉ (8)	4.4 mg
		Epothilone G ₂ (11)	9.4 mg
fraction 2	2.1	Epothilone A (1)	29800.0 mg
		Epothilone B (2)	10300.0 mg
		Epothilone C ₁ (16)	32.4 mg
	2.2	Epothilone B ₁₀ (9)	1.1 mg
		Epothilone C ₂ (18)	58.4 mg
	2.3	Epothilone D ₁ (17)	5.3 mg
		trans-Epothilone C ₁ (28)	1.4 mg
		trans-Epothilone C ₂ (28)	4.5 mg
		38	6.5 mg
		Epothilone H ₁ (12)	3.0 mg
		Epothilone C ₈ (22)	7.3 mg
	2.4	37	2.9 mg
		Epothilone C ₃ (20)	32.5 mg
		Epothilone C ₈ (26)	26.3 mg
		Epothilone D ₂ (19)	13.1 mg
		Epothilone K (36)	0.4 mg
	2.5	Epothilone C ₈ (24)	2.9 mg
		Epothilone C ₄ (21)	6.5 mg
		39	0.8 mg
	2.6	Epothilone H ₂ (13)	1.5 mg
		Epothilone D ₃ (23)	0.9 mg
		Epothilone C ₉ (27)	3.0 mg
		Epothilone C (14)	4600.0 mg
		Epothilone D (15)	2700.0 mg

PCT

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation ⁶ : C07D 493/04, 417/06, 413/06, 277/24 // (C07D 493/04, 313:00, 303:00)		A3	(11) Internationale Veröffentlichungsnummer: WO 99/65913
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(21) Internationales Aktenzeichen: PCT/EP99/04244		(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) Internationales Anmeldedatum: 18. Juni 1999 (18.06.99)			
(30) Prioritätsdaten: 198 26 988.9 18. Juni 1998 (18.06.98) DE			
(71) Anmelder (für alle Bestimmungsstaaten ausser US): GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF) [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE).			
(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): HOEFLE, Gerhard [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE). REICHENBACH, Hans [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE). GERTH, Klaus [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE). HARDT, Ingo [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE). SASSE, Florenz [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE). STEINMETZ, Heinrich [DE/DE]; Mascheroder Weg 1, D-38124 Braunschweig (DE).		Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	
(74) Anwälte: BOETERS, Hans usw.; Boeters & Bauer, Bereiteranger 15, D-81541 München (DE).		(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 20. April 2000 (20.04.00)	
(54) Title: EPOTHILONE MINOR CONSTITUENTS			
(54) Bezeichnung: EPOTHILON-NEBENKOMPONENTEN			
(57) Abstract <p>The invention relates to compounds which are obtained by fermenting DSM 6773, especially epothilones A1, A2, A8; A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 and K and trans-epothilones C1 and C2.</p>			
(57) Zusammenfassung <p>Die Erfindung betrifft Verbindungen, die durch Fermentation von DSM 6773 erhältlich sind, insbesondere Epothilone A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 und K und Trans-Epothilone C1 und C2.</p>			

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EE	Estland						

INTERNATIONAL SEARCH REPORT

Internation Application No

PCT/EP 99/04244

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D493/04 C07D417/06 C07D413/06 C07D277/24
 //(C07D493/04,313:00,303:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5 March 1998 (1998-03-05) abstract; claims; examples	1-13
X	WO 98 22461 A (BIOTECHNOLOG FORSCHUNG GMBH ;GERTH KLAUS (DE); HOEFLE GERHARD (DE)) 28 May 1998 (1998-05-28) abstract; claims; examples	1-13
X	WO 97 19086 A (BIOTECHNOLOG FORSCHUNG GMBH ;KIFFE MICHAEL (DE); HOEFLE GERHARD (D) 29 May 1997 (1997-05-29) abstract; claims; examples	1-13
	-/-	

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

22 February 2000

Date of mailing of the international search report

07/03/2000

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04244

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NICOLAOU K C ET AL: "DESIGNED EPOTHILONES: COMBINATORIAL SYNTHESIS, TUBULIN ASSEMBLY PROPERTIES, AND CYTOTOXIC ACTION AGAINST TAXOL-RESISTANT TUMOR CELLS" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, DE, VERLAG CHEMIE. WEINHEIM, vol. 36, no. 19, 1 January 1997 (1997-01-01), pages 2097-2103, XP002064441 ISSN: 0570-0833 page 2099 -page 2100	1-13
X	NICOLAOU ET AL: "Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach" CHEMISTRY - A EUROPEAN JOURNAL, US, VCH PUBLISHERS, vol. 3, no. 12, 1997, pages 1957-1970, XP002121565 ISSN: 0947-6539 page 1959 -page 1961	1-13
X	BALOG A ET AL: "Stereoselective Syntheses and Evaluation of Compounds in the 8-Desmethylepothilone A Series: Some Surprising Observations Regarding Their Chemical and Biological Properties" TETRAHEDRON LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 38, no. 26, 30 June 1997 (1997-06-30), pages 4529-4532, XP004074826 ISSN: 0040-4039 the whole document	1-13
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Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0923583 A	23-06-1999
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		CZ 9901750 A	15-09-1999
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International Aktenzeichen

PCT/EP 99/04244

A. KLASIFIZIERUNG DES ANMELDUNGSGEGENSTANDES IPK 6 C07D493/04 C07D417/06 C07D413/06 C07D277/24 //(C07D493/04, 313:00, 303:00)		
Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK		
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C. ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5. März 1998 (1998-03-05) Zusammenfassung; Ansprüche; Beispiele	1-13
X	WO 98 22461 A (BIOTECHNOLOG FORSCHUNG GMBH ;GERTH KLAUS (DE); HOEFLE GERHARD (DE)) 28. Mai 1998 (1998-05-28) Zusammenfassung; Ansprüche; Beispiele	1-13
X	WO 97 19086 A (BIOTECHNOLOG FORSCHUNG GMBH ;KIFFE MICHAEL (DE); HOEFLE GERHARD (D) 29. Mai 1997 (1997-05-29) Zusammenfassung; Ansprüche; Beispiele --- -/-	1-13
<div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen </div> <div> <input checked="" type="checkbox"/> Siehe Anhang Patentfamilie </div> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Besondere Kategorien von angegebenen Veröffentlichungen :</p> <p>"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist</p> <p>"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist</p> <p>"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)</p> <p>"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht</p> <p>"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist</p> </div> <div style="flex: 1;"> <p>"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis der Erfindung zugrundeliegenden Prinzipie oder der ihr zugrundeliegenden Theorie angegeben ist</p> <p>"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfindeterischer Tätigkeit beruhend betrachtet werden</p> <p>"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfindeterischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist</p> <p>"Z" Veröffentlichung, die Mitglied derselben Patentfamilie ist</p> </div> </div>		
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22. Februar 2000		07/03/2000
Name und Postanschrift der internationalen Recherchenbehörde Europäisches Patentamt, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 661 epo nl, Fax (+31-70) 340-3016		Bevollmächtigter Bediensteter Paisdor, B

INTERNATIONALER RECHERCHENBERICHT

International / Abkürzungen
PCT/EP 99/04244

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	<p>NICOLAOU K C ET AL: "DESIGNED EPOTHILONES: COMBINATORIAL SYNTHESIS, TUBULIN ASSEMBLY PROPERTIES, AND CYTOTOXIC ACTION AGAINST TAXOL-RESISTANT TUMOR CELLS"</p> <p>ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, Bd. 36, Nr. 19, 1. Januar 1997 (1997-01-01), Seiten 2097-2103, XP002064441 ISSN: 0570-0833 Seite 2099 -Seite 2100</p>	1-13
X	<p>NICOLAOU ET AL: "Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach"</p> <p>CHEMISTRY - A EUROPEAN JOURNAL,US,VCH PUBLISHERS, Bd. 3, Nr. 12, 1997, Seiten 1957-1970, XP002121565 ISSN: 0947-6539 Seite 1959 -Seite 1961</p>	1-13
X	<p>BALOG A ET AL: "Stereoselective Syntheses and Evaluation of Compounds in the 8-Desmethylepothilone A Series: Some Surprising Observations Regarding Their Chemical and Biological Properties"</p> <p>TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, Bd. 38, Nr. 26, 30. Juni 1997 (1997-06-30), Seiten 4529-4532, XP004074826 ISSN: 0040-4039 das ganze Dokument</p>	1-13
X	<p>SU D -S ET AL: "STRUCTURE - ACTIVITY RELATIONSHIPS OF THE EPOTHILONES AND THE FIRST IN VIVO COMPARISON WITH PACLITAXEL"</p> <p>ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, Bd. 36, Nr. 19, 1997, Seiten 2093-2096, XP002916075 ISSN: 0570-0833 Seite 2094 -Seite 2095</p>	1-13

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